Use of Botulinum Toxin in Urologic Diseases

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OnabotulinumtoxinA (onaBoNTA) is approved by the US Food and Drug Administration for the treatment of urinary incontinence due to neurogenic detrusor overactivity and for the treatment of refractory overactive bladder. As a treatment for benign prostatic hyperplasia, onaBoNTA showed no difference over placebo in recently published studies. In contrast, treating interstitial cystitis/bladder pain syndrome with onaBoNTA has shown efficacy, and the current American Urological Association guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome lists onaBoNTA as fourth-line treatment. This comprehensive review will present all studied applications of onaBoNTA within the lower urinary tract. UROLOGY 91: 21–32, 2016. © 2016 Elsevier Inc.

Botulinum toxins are produced by *Clostridium botulinum*, and they selectively disrupt neurotransmission in both striated and smooth muscle.[1] Of the 7 serotypes of botulinum toxins, serotypes A and B are the two that are commercially available. After botulinum toxin (BoNT) is internalized by presynaptic neurons, it cleaves the synaptosome-associated protein 25 kDa within the synaptic fusion complex to inhibit acetylcholine exocytosis into the neuromuscular junction.[2] As such, BoNT inactivates cholinergic transmission and causes temporary muscle denervation. Additionally, BoNT is thought to affect afferent neurotransmission within the bladder by inhibiting the release of adenosine triphosphate and substance P with a reduction in the axonal expression of purinergic and vanilloid receptors.[3] Thus, the action of BoNT on both efferent and afferent nerves within the bladder helps to explain its long-lasting effects.

The use of BoNT within the urinary tract was first described by Dykstra et al in 1988 as a treatment for detrusor sphincter dyssynergia (DSD).[4] Schurch et al first reported injecting BoNT into the bladder of 21 spinal cord injury (SCI) patients with severe neurogenic detrusor overactivity (NDO) and urge urinary incontinence (UUI).[5] Subsequently, two phase 3 placebo-controlled randomized controlled trials (RCTs) performed by Ginsberg et al and Cruz et al led to the 2011 US Food and Drug Administration (FDA) approval of onabotulinumtoxinA (onaBoNTA) for the treatment of UUI due to NDO.[6,7] Compared to placebo, onaBoNTA 200 units (U) injected into the detrusor decreased mean UUI in SCI and multiple sclerosis (MS) patients with NDO. Furthermore, two phase 3 placebo-controlled RCTs performed by Nitti et al and Chapple et al led to the 2013 FDA approval of onaBoNTA for the treatment of overactive bladder (OAB) refractory to anticholinergics.[8,9] Compared to placebo, a 100 U dose of onaBoNTA injected into the detrusor decreased mean UUI in both studies.

Other applications for BoNT include benign prostatic hyperplasia (BPH) and interstitial cystitis/bladder pain syndrome (IC/BPS). McVary et al performed a large RCT comparing onaBoNTA 200 U to placebo, and no differences were seen with onaBoNTA compared to placebo in International Prostate Symptom Score (I-PSS).[10] As a treatment for IC/BPS, BoNT has shown efficacy. Kuo and Chancellor performed an RCT in IC/BPS patients comparing hydrodistention with either 100 U or 200 U doses of onaBoNTA vs hydrodistention alone, and they found that bladder pain and bladder capacities significantly improved only in the BoNT groups vs the control group, $P = .002$.[11] Off-label use of BoNT has been listed as a fourth-line treatment in the current American Urological Association (AUA) guideline for the treatment of IC/BPS.[12]

BOTULINUM TOXIN FOR NEUROGENIC DETRUSOR OVERACTIVITY

NDO is characterized by the presence of involuntary detrusor contractions (IDCs) during filling cystometry in patients with neurologic diseases such as MS or SCI.[13] Because NDO causes reduced bladder capacity and UUI, quality of life (QOL) is often impaired. In addition, long-term anticholinergic treatment for NDO remains ineffective because of a lack of efficacy and intolerable side effects such as dry mouth and constipation, both of which are already baseline problems in neurogenic bladder patients.[14] Early single-institution and small multi-institutional placebo-controlled RCTs of onaBoNTA in NDO patients showed improvements in both UUI and QOL.[15,16] Subsequently, Allergan performed 2 multicenter, placebo-controlled, phase 3 RCTs to further study the efficacy and tolerability of onaBoNTA in the treatment of NDO (see Table 1).[6,7]

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Table 1. onaBoNTA NDO clinical trials

Reference	Design	Follow-up (f/u)	N	Treatment Arms	Outcome Measures (1 – Primary, 2 – Secondary)	D/C	Primary Efficacy Measure	UDS Secondary Efficacy Measures	Dry Rate	I-QOL Total Score	Adverse Events
Cruz et al[7]	Double-blind RCT comparing onaBoNTA 200 U and 300 U to placebo in NDO patients with UUI	≥52 weeks or ≥12 weeks after second treatment	275	Placebo: 92 OnaBoNTA 200 U: 92 OnaBoNTA 300 U: 91	1-Weekly UUI episodes at week 6 2-UDS (MCC, Peak Pdet, Compliance) and I-QOL score	Total: 45 (from AEs: 5)	200 U BoNTA Decrease by 21.8 UI weekly episodes 300 U BoNTA Decrease by 19.4 UI weekly episodes Placebo Decrease by 13.2 UI weekly episodes $P < .01$ for BoNTA vs placebo	MCC: Increase 157 cc for BoNTA 200 U vs 6 cc for placebo Peak Pdet: Decrease 28.5 cmH_20 for BoNTA 200 U vs 6 cmH_20 for placebo $P < .001$ for BoNTA vs placebo	MS: 43% for 200 U and 41% for 300U vs 12% placebo SCI: 31% for 200 U and 37% for 300 U vs 2% placebo $P < .001$ for BoNTA vs placebo	Placebo: 11-point increase 200 U BoNTA: 24-point increase 300 U BoNTA: 24-point increase $P < .001$ for BoNTA vs placebo	– UTI most common – CIC initiated in 30% for 200 U and 54% for 300 U – No Abs – No respiratory compromise
Ginsberg et al[6]	Double-blind RCT comparing onaBoNTA 200 U and 300 U to placebo in NDO patients with UUI	≥52 weeks or ≥12 weeks after second treatment	416	Placebo: 149 OnaBoNTA 200 U: 135 OnaBoNTA 300 U: 132	1-Weekly UUI episodes at week 6 2-UDS (MCC, Peak Pdet, Compliance) and I-QOL score	Total: 87 (from AEs: 13)	200U BoNTA Decrease by 21 UI episodes 300 U BoNTA Decrease by 23 UI weekly episodes Placebo Decrease by 9 UI weekly episodes $P < .001$ for BoNTA vs placebo	MCC: Increase 151 cc for BoNTA 200 U vs 16 cc for placebo Peak Pdet: Decrease 35 cmH_20 BoNTA 200 U vs 2 cmH_20 for placebo $P < .001$ for BoNTA vs placebo	Placebo: 10% both SCI and MS 200 U BoNTA: 36% both SCI and MS 300 U BoNTA: 41% both SCI and MS $P < .001$ for BoNTA vs placebo	Placebo: 9-point increase 200 U BoNTA: 31-point increase 300 U BoNTA: 33-point increase $P < .001$ for BoNTA vs placebo	– UTI most common – CIC initiated in 35% for 200 U and 42% for 300 U – No Abs – No respiratory compromise

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